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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/297,040	07/21/1999	PETER MOSE LARSEN	2012.0390004	9201

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STERNE KESSLER GOLDSTEIN & FOX
1100 NEW YORK AVENUE NW
SUITE 600
WASHINGTON, DC 200053934

EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 05/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/297,040	MOSE LARSEN ET AL.	
	Examiner	Art Unit	
	Samuel W. Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,9,12-18,20,21,24-32 and 34-39* is/are pending in the application.

4a) Of the above claim(s) *-5, 9, 12-18, 20-21 and 24-27 and 34-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

Claims 1-5, 9, 12-18, 20-21, 24-32 and 34-39 are pending.

Applicants' amendment filed 3/22/05, which amends claims 28 and 32, cancels claim 33, and the applicants' request (filed 3/22/05) for extension of time of three months, have been entered. Note that claims 6-8, 10-11, 19 and 22-23 were canceled by the applicants' amendment filed 8/6/04. Claims 1-5, 9, 12-18, 20-21 and 24-27 and 34-39 are withdrawn from further consideration by the Examiner (for the reason, please see the Office action mailed 9/22/04). Thus, the pending claims 28-32 are examined in this Office action.

The previous rejection under 35 USC, second paragraph is withdrawn because of the applicants' amendment to claim 32. Yet, the following rejection is applicable to the amended claim 28.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 28-32 are again rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 28 as *amended* recites "*protective diabetes mediating protein*"; the recitation is not apparent and not apparent as to whether or not said protein has activity of mediating both diabetes state and a protective activity (note that the recitation does not make it clear that what is

protected), or, has a activity for protecting the diabetes mediating state, or, has a protective activity against diabetes. The dependent claims are also rejected.

The following rejection under 35 USC, first paragraph are maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-32 are again rejected under 35 U.S.C. 112, first paragraph, because the specification, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not describe a method of preventing a diabetes state in a subject comprising administering to said subject a protein variant comprising amino acid sequence that has at least 90% (claim 28) or 95% (claim 30) sequence identity to the full-length sequence of SEQ ID NO:4 (human galectin-3). The specification does not teach the variant protein has activity ameliorating or preventing a diabetes state. Thus, applicants are not in possession of the claimed method.

While applicants may wish to amend the claims in such a way that the variant of 95% or 90% sequence identity to full-length SEQ ID NO:4 which has assayable function, nevertheless such the amendment still cannot overcome the enablement rejection to the claimed method (see below).

Claims 28-32 are again rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is directed to a method of preventing or treating a subject suffering from a diabetes disorder comprising administering to the subject a protein composition comprising the full-length SEQ ID NO:4, or a protein variant having at least 90% or 95% sequence identity to SEQ ID NO:4. In Example 8, the specification states that galectin-3 expression was significantly down-regulated at onset of IDDM (see pages 48-49). Based on this statement, the galectin-3 has a putative role in treating a diabetes disorder. It should be noted that there are a large number of proteins involved in the development of the diabetes disorder. The art teaches that down-regulation of a protein does not necessarily correlate with a potential of said protein being used for treating or preventing the diabetes. For instance, tumor necrosis factor-alpha (TNF-α) has been known to induce a diabetes state; yet, the TNF-α expression level which is at least not elevated but appears to be down-regulated in patients suffering from a diabetes (see Table 1 of Bluher, M. et al. reference: *Diabetes Care* (2001), 24, 328-334). This suggests that there necessarily is no correlation between down-regulation of a protein (expression regulation) and therapeutic use (treatment or prevention) of said protein. The specification at best suggests that the galectin-3 expression *regulation* occurs when diabetes develops but not adequately disclose how to prevent said diabetes using the claimed composition. Thus, given the unpredictability of the field of the invention, the relative lack of information of human galectin-3

protein having an ability of preventing a diabetes, one skilled in the art would be unable to practice the claimed invention without the exercise of undue experimentation.

The applicants' response to the rejection under 35 USC 112, first paragraph

The response filed 3/22/05 argues that the specification on page 17 has provided the description regarding the protein variant which has 90% or 95% sequence identity to the full-length sequence of SEQ ID NO:4 (human galectin-3). The argument is found to be unpersuasive because the specification does not describe that the said variant has activity of treating or/and preventing a diabetes state.

On pages 12-13, the response discusses the issue regarding the galectin-3 protein regulation, i.e., decrease of galectin-3 expression at onset of IDDM (a diabete state) and increase of galectin-3 expression in non-diabete subject (Example 8). Thus, the response infers that there is evidence that the galectin-3 is a protein protecting a subject against or ameliorating diabetes in human (see the 3rd paragraph of page 13). In addition, the response asserts that examiner's rejection to the claims is based solely on down-regulation of the galectin-3 expression (see page 13).

The applicants' arguments have been fully considered but they are found to be not persuasive because of the reasons stated in the above rejection and the reasons set forth below. The down- or/and up- regulation of the galectin-3 expression in a subject tissue *per se* does not sufficiently provide solid evidence that the galectin-3 prevents the subject from diabetes. Note that the prevention is distinct/different from treatment which refers to a complete inhibition of occurrence of a disease or disorder state/condition. Neither the prior art nor does the

specification teach that the galectin-3 protein completely inhibits a diabete state. The current invention enables a method of ameliorating or treating diabetes, but NOT preventing the diabetes, comprising administering to a patient (subject) the full-length galectin-3 protein. Note that the specification emphasizes the down-regulation by use the term "significantly" (see "Gal-3 expression was significantly down-regulated at day 7 and at onset of IDDM" on the bridging paged 48-49 of the specification), suggesting that the down-regulation is a dominant event over up-regulation. Therefore, the claim rejection under 35 USC 112, first paragraph (the Office action mailed 2/6/04) discuses relation of this down-regulation to *prophylactic* role of gal-3. Also, note that the prior art has shown that down-regulation of a protein (e.g., TNF-α) that induces in diabetic development, in a patient per se is not necessarily linked to preventing diabetes (see the Office action mailed 9/22/04).

As for the up-regulation, the response asserts (see page 13, the second paragraph) that Gal-3 expression increases in vitro IL-1β stimulated islet from animals which did not develop diabetes, and thus infers that the Gal-3 has the preventive role against diabetes.

The applicants' argument is found to be unpersuasive because up-regulation (i.e., increase) of Gal-3 expression is not necessarily correlated with therapeutic activity or/and the *prophylactic* role of the Gal-3 protein. Wachlin et al. (*J. Autoimmun.* (2003) Vol. 20, pages 303-312, see Table 2 and page 307, the right column) teach that in an IL-1β-stimulated pancreatic islets from rat that does not develop diabetes (i.e., diabetes resistant), expression of a protein, the surface receptors intercellular adhesion molecule (ICAM)-1, is markedly increase; prior art in record does not demonstrate/teach ability of the said protein to prevent diabetes. Therefore, the up-regulation of a protein per se is not considered to be evidence providing a significant support for the protein

prevention of a disease/disorder state. And, thus, Example 8 provides insufficient evidence for the protective role of the Gal-3.

On page 13, the 3rd paragraph, the response sets forth the instance of galectin-3 expression in rat insulinoma (RIN) cell wherein the Gal-3 expression exhibits an increased proliferative rate and the expression renders said cell more resistant to a negative effect of cytokine, e.g., IL-1 β (see page 39 of the specification) so as to support the preventive role of the Gal-3. The applicants' argument has been found to be not persuasive because the increase of cell proliferation and resistance to negative effect of the cytokine are not considered to be specifically or directly correlated with prevention of a diabetic state. Many proteins/enzymes involved in regulating the cellular proliferation and the cytokine activity. The statement "more resistance to negative effect of cytokine" does not provide evidence that Gal-3 protein can completely inhibit (i.e., prevent) occurrence of the diabetes. The burden is on the applicants to show how said resistance in RIN cell results in preventing diabetes in human.

On pages 13-14, the response further discusses that galectin-3 deficiency results in accelerated diabetic glomerupathy, which is associated with accumulation of advanced glycation end products (AGEs), and that the galectin-3 acts as an AGE receptor to protect from AGE-induced tissue injury (see the 1st paragraph, page 14 of the response); and thus, the applicants infer that the galectin-3 can prevent the diabetes thereof.

The applicants' argument is found to be not persuasive because without animal model, the mechanism of galectin-3 protein binding to the AGE molecule and/or action of protecting from AGE-induced tissue injury by the protein thereof *per se* does not establish a role of the galectin-3 preventing diabetes (note that herein, "protect" is not equal to "prevent"). The burden is on the

applicants to show the AGE induced tissue injury can completely inhibit/obstruct (i.e., prevent) a diabetic state in a subject.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

Karen Cochrane Carlson PhD

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER

Samuel Wei Liu, Ph.D.

May 5, 2005